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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,858	04/20/2001	S. Gary Mansfield	A31304-BAD 072874.0154	4422

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,858	MANSFIELD ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. The election restriction requirement set forth in the previous office action is withdrawn in response to Applicant's arguments filed 10-20-03.

Priority

2. On page 1 of the specification as filed, Applicants improperly state that the filing date of provisional application number 60/008,317 is 12-15-1995. According to PTO records the filing date should state 12-07-1995.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does not reasonably provide enablement for producing a chimeric in a cell *in vivo* for therapeutic treatment of conditions associated with defects in the coding region of the factor VIII gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The instant claims read on a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a factor VIII pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The specification as filed provides only sufficient guidance and/or instruction for using the claimed nucleic acid constructs to produce chimeric mwithin a cell in an *in vitro* environment, wherein said constructs are used to produce a chimeric mRNA. However, the specification as filed does not provide sufficient guidance such that the ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the compounds of the instant claims to treat conditions associated with defects in the coding region of the factor VIII gene, in a method of gene therapy.

There are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of

the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated. Additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs that would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

It is noted that the instant application claims priority back to 12/07/1995, and that at the time the invention was made the state of the prior art indicated that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (Science, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "'[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, column 2).

In the instant case, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre-trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the

invention was made provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the factor VIII gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claim(s) 1-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,013487 in view of De Brasi et al. (Medicina, 1996, Vol. 56 (5/1), English abstract). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, and claims 1-34 of U.S. Patent No. 6,013487 are both directed to a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a target pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The claims of the instant application differ from the issued claims in that claim the instant claims are specifically limited to wherein the target pre-mRNA is factor VIII pre-mRNA.

The claims of the instant application are limited to a species of the broad class of "target pre-mRNAs" encompassed by the claims of the issued US Patent. The issued US Patent makes no mention of factor VIII as a target pre-mRNA.

De Brasi et al. teach that hemophilia A is a common genetic disease that is associated with mutations in the factor VIII gene.

It would have been obvious at the time the invention was made to design nucleic acid constructs expressed in cells according to the present invention wherein said constructs target pre-mRNA encoding factor VIII. One of ordinary skill in the art would have been motivated to make this modification in an effort to produce potential chimeric RNA that would potentially function as therapeutics to correct defects in the factor VIII gene, and thereby further elucidate its role in the development of hemophilia.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE